Editorial

Non-invasive assessment of endothelial function

Risk assessment and clinical management of patients with coronary artery disease (CAD) has traditionally concentrated on the anatomical features of atherosclerosis. Over the past decade, however, the importance of the dynamic aspects of vascular physiology, particularly the role of the endothelium, have become clear. In 1980, Furchgott demonstrated the production of a relaxant factor from healthy endothelium (EDRF),[1] which has subsequently been characterised as nitric oxide or a related molecule.[2] Nitric oxide is not only an important physiological vasodilator[3] counteracting the effect of vasoconstrictors but it also inhibits platelet activation, monocyte–endothelium cell interactions, and smooth muscle cell proliferation and migration.[4] Studies in patients with established CAD have used pharmacological and physiological stimuli to examine coronary vascular tone and flow responses which are dependent on endothelial production of nitric oxide.[5 6] These studies have shown marked abnormalities in coronary vasoreactivity in atherosclerotic vessels, which may be the basis for disturbances of coronary supply involved in the genesis of many episodes of transient myocardial ischaemia.[7] This represents a target for therapy as reduction of risk factors such as hypercholesterolaemia, which may result in dysfunctional endothelium, have recently been shown to reduce the activity of transient myocardial ischaemia.[8] Furthermore, dysfunctional vascular endothelium may play a role in plaque destabilisation and the risk of acute coronary events.[9] Improvement in endothelial dysfunction at the site of atherosclerotic plaques may therefore contribute to the impressive decrease in clinical events seen in large prospective clinical trials of cholesterol lowering in both primary and secondary prevention.[10 11]

While CAD normally presents from middle age onwards, morphological evidence of atherosclerosis has been detected as early as the first two decades of life.[12] This early atherosclerosis is associated with a similar risk factor profile to that seen in patients with CAD, and epidemiological evidence suggests that the damaging effects of risk factors in early life are related to coronary morbidity and mortality decades later.[13] Strategies which aim to retard the progression of atherogenesis from an earlier stage may, therefore, have a substantial impact on the subsequent incidence of clinical disease. This approach is supported by the continuing high incidence of cardiovascular events in patients with CAD despite active treatment.

Endothelial dysfunction is now recognised as a key early event in atherogenesis.[14] The failure of the endothelium dependent vasodilatory responses of large conduit arteries to physiological stimuli is likely to represent either decreased production or increased inactivation of nitric oxide. Experimental evidence has demonstrated that endothelial derived nitric oxide may be an important endogenous antiatherogenic molecule and that reduction in nitric oxide activity may facilitate the progression of atherosclerosis.[15] In addition to loss of the protective actions of nitric oxide, endothelial dysfunction may result in a number of abnormalities which may enhance progression of atherosclerosis including: increased release of vasoconstrictor substances; expression of surface adhesion molecules which facilitate monocyte recruitment and egress into the intima; production of growth factors which promote vascular smooth muscle cell proliferation and migration; and enhanced thrombogenicity mediated by increased platelet activation, plasminogen activator inhibitor-1, and expression of tissue factor.[14]

Research on the benefit of early intervention has been limited by the lack of a clinical marker of atherogenesis which could be used to identify groups or individuals with early disease and to measure the effects of intervention. While endothelial dysfunction has been demonstrated in patients with risk factors for CAD and angiographically normal coronary arteries,[16] the invasive nature of coronary angiography precludes its use for investigation of endothelial function during the long preclinical stage of atherosclerosis. Plethysmography can be used to measure alteration in blood flow and peripheral vascular tone in response to stimuli as an indirect assessment of resistance vessel endothelial function.[17] Abnormalities in association with risk factors similar to those described in coronary arteries have been demonstrated, although the relevance of these to abnormalities of endothelial function in conduit arteries and the progression of atherosclerosis is unclear.

Recently, novel non-invasive techniques have been developed that, using high resolution external ultrasound, permit in vivo assessment of conduit artery vascular responses in subjects as young as five years of age.[18–20] Based on a similar experimental principle to that employed in invasive coronary artery studies, vascular reactivity in response to endothelium dependent and independent stimuli are contrasted in large peripheral conduit arteries. Increased blood flow resulting in augmented shear stress is used as the physiological stimulus to endothelium dependent dilatation. Experiments in vivo using specific antagonists of nitric oxide production have indicated that flow mediated dilatation depends on release of nitric oxide from conduit artery endothelium.[21] Arterial diameter (usually the brachial or radial artery in adults and the femoral artery in smaller children) is measured at rest and following a brief period of reactive hyperaemia induced by suprasystolic inflation of a cuff (distal to the site of measurement) for several minutes followed by release. Flow mediated dilatation is expressed as a percentage of the resting vessel diameter and this response is compared to measurements of vessel dilatation induced by sublingual nitroglycerin, an endothelium independent dilator. Attenuated brachial artery flow mediated dilatation correlates with the presence of coronary endothelial dysfunction and atherosclerosis, assessed by angiography, highlighting the systemic nature of vascular disease.[22] The technique is both reproducible and reliable,[23] requires little specialised equipment outside that found in most district general hospitals, and has been applied to both cross sectional and longitudinal studies. These studies have examined the relation between classical vascular risk factors and endothelial function in young subjects in the absence of detectable atherosclerotic plaques. Impaired endothelium dependent vasodilatation has been demonstrated in asymptomatic subjects with hypercholesterolaemia,[18] insulin dependent[24] and non-insulin dependent diabetes mellitus,[20]

in both passive[25] and active smokers,[19] in subjects with homocystinuria,[26] and with advancing age in men and postmenopausal women.[27] Furthermore, a positive correlation between the severity of these risk factors and the degree of endothelial dysfunction as well as interaction between risk factors similar to that seen in population outcome studies can be demonstrated.[28] More recently these techniques have been applied to assess vascular compliance and distensibility which may also depend on endothelial derived nitric oxide.[20]

The recognised antiatherogenic properties of intact endothelium and their loss prior to the development of detectable atherosclerotic plaque, suggests that endothelial dysfunction may not be simply a marker of early vascular disease but that it may represent the primary vascular wall injury that initiates the atherosclerotic process. The mechanisms by which endothelial cell function is altered in the presence of risk factors remains unclear. Increased oxidative stress and the oxidation of low density lipoprotein may be an important common pathway of injury,[29] although it is likely that additional mechanisms (and therefore their treatment) may vary in different risk factor groups. Increased understanding of these early events may lead to novel approaches to the retardation of the disease process, in particular aimed at the restoration of dysfunctional endothelium. Recent studies have demonstrated improvements in endothelium dependent dilatation in young asymptomatic subjects with hypercholesterolaemia following dietary supplementation with L-arginine,[30] the precursor of nitric oxide, and experimental studies in hypercholesterolaemic animals suggest that L-arginine may decrease or even reverse atherogenesis.[31] To date, however, there are no clinical trials correlating the presence of endothelial dysfunction at an early stage with later morbidity or mortality and, therefore, the validity of this treatment approach in humans remains unproven. However, interventions which decrease the incidence of cardiovascular events including cholesterol lowering, antioxidants, hormone replacement therapy in postmenopausal women, and exercise have also been shown to improve endothelial function,[32–36] suggesting a link between endothelial dysfunction and the subsequent incidence of cardiovascular events.

Abnormalities of vascular function are likely to be major determinants of atherosclerotic disease activity and progression at both an early and advanced stage. The assessment of endothelial dependent vasodilatation may provide an insight into the crucial early stages of atherogenesis and the mechanisms by which risk factors cause vascular damage. High resolution ultrasound provides a non-invasive and convenient method for the serial evaluation of vascular function enabling the study of preclinical subjects, their response to interventions, and the impact of endothelial function on subsequent clinical vascular events.

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